



NATIONAL TOXICOLOGY PROGRAM

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May 18, 2007

To: NTP Board of Scientific Counselors

From: Director, Office of Chemical Nomination and Selection, Environmental Toxicology Program

Subject: New Toxicology Study Nominations for Review

The following material is provided as background for the June 22, 2007 NTP Board of Scientific Counselors (BSC) meeting and concerns new nominations for NTP toxicological studies. The BSC is asked to review the nominations under consideration with respect to the attached charge.

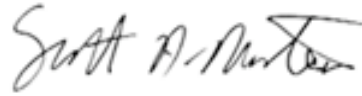
The NTP has a formal multi-step process for reviewing new study nominations before selections for testing are made and studies are initiated. The first external step in this process is a review by the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC). The ICCEC reviewed nine new study nominations in December 2006. The preliminary study recommendations for these nominations and a request for public comment were published in the *Federal Register* March 29, and through the NTP's newsletter and website. The NTP identified four of these new study nominations for review by the BSC at the June 22 meeting: artificial butter flavoring mixture and certain components; asbestos, naturally occurring and atypical forms; nanoscale silver; and o-phthalaldehyde. The remaining nominations will be reviewed by the BSC at the next scheduled meeting.

The four nominations under consideration and the corresponding preliminary study recommendations are summarized in the attached table. Draft Research Concepts have been prepared by NTP staff for these nominations and are also enclosed. Research concepts are brief documents describing the NTP's proposed approach to address the preliminary study recommendations for each nomination.

This is the first time the BSC is asked to consider the initial thoughts of the NTP (Draft Research Concepts) concerning studies that may be performed to address a given nomination. While the role of the BSC in providing guidance on whether a given nomination warrants expenditure of government funds is not changing, we are hoping to benefit from the additional comments of the BSC, *ad hoc* experts, and the public on the Draft Research Concepts that will be presented for consideration.

A description of the NTP's study nomination procedures, the March 29 *Federal Register* notice, public comments, and background documents supporting each of these new nominations are provided on the enclosed CD, and are also available electronically on the NTP web site at <http://ntp.niehs.nih.gov/go/29287>.

Please contact me by telephone at (919) 541-5710 or by email at masten@niehs.nih.gov if prior to the June 22 meeting you have questions or comments regarding any of the nominations or background material.

A handwritten signature in black ink, appearing to read "Scott A. Masten". The signature is fluid and cursive, with the first name "Scott" being more prominent.

Scott A. Masten, Ph.D., DABT

Enclosures

New Nominations for NTP Toxicological Studies, May 2007

Substance [CAS No.]	Nominated by	Nomination Rationale (Principles *)	Preliminary Study Recommendations*****	Public Comments Received
Artificial butter flavoring mixture and certain components: Acetoin [513-86-0] Diacetyl [431-03-8]	United Food and Commercial Workers International Union	Evidence of lung disease in exposed workers and respiratory toxicity in short-term animal toxicity studies (1, 5, 7)	-Chronic toxicity and carcinogenicity studies via inhalation in rats -Mechanistic studies	Joseph Manuppello and Samantha Dozier, People for the Ethical Treatment of Animals, and Kristie M. Stoick, Physicians Committee for Responsible Medicine John B. Hallagan, Flavor and Extract Manufacturers Association of the United States
Asbestos, naturally occurring and atypical forms [1332-21-4]	National Center for Environmental Health/Agency for Toxic Substances and Disease Registry U.S. Environmental Protection Agency	Widespread community exposure in certain geographic locales; insufficient dose-response data to characterize risk from exposure to “unregulated” asbestiform mineral fibers and naturally occurring fibrous mineral “mixtures” (1, 2, 6, 7)	-Mineral characterization - <i>In vitro</i> durability and toxicity studies -Subchronic and chronic toxicity/carcinogenicity studies via inhalation -Studies should utilize test materials representative of minerals identified in Libby, MT and at other Naturally Occurring Asbestos (NOA) sites	Joseph Manuppello and Samantha Dozier, People for the Ethical Treatment of Animals, and Kristie M. Stoick, Physicians Committee for Responsible Medicine John W. Kelse, R.T. Vanderbilt Company, Inc. William C. Ford, National Stone, Sand & Gravel Association Michelle Wyart-Remy, Industrial Minerals Association-Europe, and Mark G. Ellis, Industrial Minerals Association-North America
Nanoscale materials Nanoscale gold [7440-57-5] Nanoscale silver [7440-22-4]	U.S. Food and Drug Administration	Widespread and increasing use in drug, food and cosmetic products; lack of adequate toxicological and pharmacokinetic data; need to evaluate whether the current required tests are adequate to detect adverse biological and toxicological events (1, 6, 7)	-Nanoscale materials characterization -Metabolism and pharmacokinetic studies -Acute, subacute and subchronic toxicity studies -Mechanistic studies to assess the role of size and surface coating on biological disposition and toxicity	Joseph Manuppello and Samantha Dozier, People for the Ethical Treatment of Animals, and Kristie M. Stoick, Physicians Committee for Responsible Medicine Michael F. Cole, Nano Testing Consortium Michael DiRienzo, The Silver Institute

Substance [CAS No.]	Nominated by	Nomination Rationale (Principles*)	Preliminary Study Recommendations*****	Public Comments Received
<i>o</i> -Phthalaldehyde [643-79-8]	National Institute for Occupational Safety and Health	Widespread and increasing use as a disinfectant in health care settings; lack of adequate and publicly available toxicological data; potential skin and respiratory sensitizer (1, 6, 7)	-Toxicological characterization including studies to assess dermal irritation, dermal toxicity, and sensitization and asthmagenic potential	Joseph Manuppello and Samantha Dozier, People for the Ethical Treatment of Animals and Kristie M. Stoick, Physicians Committee for Responsible Medicine

*Nomination Principles for NTP Studies

The NTP is an interagency program whose mission is to evaluate chemical, biological, and physical agents (collectively referred to as “substances”) of public health concern by developing and applying tools of modern toxicology and molecular biology. The NTP operates under the general principle that industry will evaluate substances for health and environmental effects as intended and mandated by Congress under legislative authorities. Therefore the NTP, acting to carry out its mission, solicits nominations for NTP studies from the following categories:

1. Substances found in home, workplace, or ambient environments that are not associated with a single commercial organization.
2. Naturally occurring substances that may not be adequately evaluated without federal involvement.
3. Commercial products with significant exposure that were first marketed prior to current testing requirements or those that generate too little revenue to support further evaluations.
4. Potential substitutes for existing chemicals or drugs that might not be developed without federal involvement.
5. Mixtures of substances for which evaluations are not required of industry.
6. Substances that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities.
7. Substances that should be evaluated to improve the scientific understanding of structure-activity relationships and thereby help limit the number of substances requiring extensive evaluations.
8. Emergencies or other events that warrant immediate federal government evaluation of a substance.

Prior to committing to specific studies, the NTP assesses the needs for studies by: evaluating existing literature and testing data, assessing ongoing evaluations in the government and private sector, and determining how the nomination fits into an overall plan for improving current test methods. The selection of a substance or issue for study by the NTP does not automatically commit the NTP to its evaluation. The NTP considers priorities for nominated studies at many phases: when the nomination is reviewed and evaluated for possible study, when the study is being designed, and again when the NTP considers the most appropriate intramural or extramural mechanism to conduct the study. The NTP may defer a study during any of these phases if suitable data become available, if higher priority studies are identified, or if the study proves to be impractical.

** The term “toxicological characterization” in this table includes studies for genotoxicity, subchronic toxicity, and chronic toxicity/carcinogenicity as determined to be appropriate during the conceptualization and design of a research program to address toxicological data needs. Though other types of studies (e.g., metabolism and disposition, immunotoxicity, and reproductive and developmental toxicity) may be conducted as part of a complete toxicological characterization, these types of studies are not listed unless they are specifically recommended.

*** Preliminary study recommendations are developed and refined by the nominator, NTP staff, and the NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC).

Charge for NTP Board of Scientific Counselors (BSC) Review of NTP Study Nominations and Draft Research Concepts

A group of new study nominations is being presented to the BSC for review and comment. The NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) reviewed these nominations and preliminary study recommendations were developed for each nomination. Following the ICCEC review, public comments were solicited on the nominations and preliminary study recommendations. NTP staff scientists then use the preliminary study recommendations to guide the initial development of a proposed research program for each nomination. The NTP asks the BSC to:

- provide its general views on the merit of these study nominations.
- advise whether the proposed study approach or any additional studies are an appropriate use of the NTP's resources.
- offer its perspective on any public comments received on these nominations.

This public meeting also provides an additional opportunity for program staff and the BSC to receive public comment on these nominations.

Action requested:

The BSC will review and comment on a draft NTP research concept. A research concept is a brief document outlining the nomination rationale, and the significance, study approach, and expected outcome of a proposed research program tailored for each nomination.

Specific charge questions:

- Does the NTP research concept address the needs of the nomination?
- Is the proposed study approach as outlined in the research concept document appropriate in scope given the merit of the nomination? Are there other studies that should be considered for this substance?
- Does the proposed research program address an important area of biomedical research (e.g. children's health, genetic susceptibility, specific environmental disease) and/or advance the field of environmental health sciences?
- Do the nomination and proposed research program merit NTP evaluation, and if so, what priority (low, moderate, or high) should it be given?

Review materials provided:

- Summary table of nominations and preliminary study recommendations
- Nomination supporting documents (on CD only)
- Public comments received (on CD only)
- NTP research concepts